REMARKS

Claims 1-2 and 4-20 are pending in the instant application. Claims 1, 2 and 4-20 have been rejected. Claims 11 and 16-20 have been canceled. Claims 1 and 15 have been amended. No new matter has been added by these amendments to the claims. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1, 2 and 11 have been rejected under 35 U.S.C. 102(b) as being anticipated by Ray et al. (1995). The Examiner suggests that Ray et al. disclose oligonucleotides that meet the structural limitations of the claims. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims to recite antisense compounds targeted to a specific region within the sequence of a specific form of inhibitor-kappa B-R (SEQ ID NO: 10). Support for this amendment to the claims can be found throughout the specification as filed but in particular at pages 80-84, Table 1.

Ray et al. (1995) disclose the use of an antisense compound targeted to the full sequence of inhibitor-kappa B-R. No other antisense compounds are taught or suggested by this reference, including those targeted to a specific region within the sequence of SEQ ID NO: 10 as now claimed. In order to anticipate an invention, the cited reference must teach each and every limitation of the claims (MPEP 2131). The cited reference fails to teach the limitations of the claims as amended. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1, 2 and 11 have been rejected under 35 U.S.C. 102(b) as being anticipated by Norman et al. (2000). The Examiner suggests that this reference discloses oligonucleotides that meet the structural requirements of the claims. Applicants respectfully disagree with the Examiner=s suggestion regarding this reference.

Review of the reference by Norman and Barton (2000) failed to reveal the teaching of any antisense oligonucleotides targeted to inhibitor-kappa B-R, including none targeted to a specific region within the sequence of SEQ ID NO: 10 as now claimed. This reference teaches the isolation of the inhibitor-kappa B-R gene

and the differences between that gene and other IKB genes. Nowhere was an antisense compound described as suggested by the Examiner. In order to anticipate an invention, the cited reference must teach each and every limitation of the claims (MPEP 2131). The cited reference fails to teach the limitations of the claims as filed. Accordingly, withdrawal of this rejection is respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Norman et al. (2000) in view of Monia et al. (US Patent 5,977,341) and Monia et al. (US Patent 6,395,545). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill in the art to make antisense targeted to inhibitor-kappa B-R since it has been taught in the art that this gene is involved in the NfkB pathway and both of the references of Monia et al. teach use of antisense to elucidate the function of members of this pathway, while the sequence of the inhibitor-kappa B-R gene is taught by Norman et al. The Examiner suggests that since the art has shown the successful use of antisense with

members of the overall pathway that it would have been obvious to use antisense to test the properties of a new pathway member. Applicants respectfully disagree with the Examiner=s suggestion regarding this combination of art.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations.

As discussed *supra*, and as acknowledged by the Examiner, the primary reference of Norman et al. (2000) fails to teach antisense oligonucleotides targeted to inhibitor-kappa B-R. The secondary references cited by the Examiner also fail to teach or suggest antisense compounds targeted to the specific gene claimed, inhibitor-kappa B-R, a point that is also acknowledged by the Examiner. Therefore, the limitations of the claims as filed and as now amended, which specify a specific region within

the sequence of inhibitor-kappa B-R (SEQ ID NO: 10) to be targeted by antisense compounds, are not taught or suggested by any of the references individually or when combined. Therefore, the limitations of the claims as amended clearly are not taught or suggested by the combination of prior art references, nor is any expectation of successful use of such antisense compounds provided by the combination of prior art. It is only with the specification in hand that one of skill would understand that a specific region of inhibitor-kappa B-R as claimed could be targeted successfully with antisense compounds. The teaching of antisense to an entirely different gene, even though it is a related gene, would not assure one of skill in the art that antisense would be successfully used. Thus, the combination of prior art cited cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 15-20 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner suggests that the specification does not provide adequate guidance for one of skill to practice the instant invention as claimed. The Examiner cites several articles to support the position that antisense therapy is an unpredictable art. Applicants respectfully traverse this rejection.

Applicants disagree with the Examiner=s suggestion that cited references support the position that application of antisense *in vivo* as a pharmaceutical is unpredictable.

The Examiner has pointed to three articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Jen and Gewirtz (2000) is a review paper on the evolution of technology to suppress gene expression, including antisense technology, and its use in human disease. Nowhere does this paper teach or suggest that antisense compounds identified from well-designed *in vitro* studies would be inherently unpredictable when used *in vivo*.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Agrawal et al. (1996) is another review paper on the technology of antisense. Although it discusses issues related to development of successful antisense compounds, nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

However, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 15 to recite that the method is an *in vitro* method. Claims 16-20 have been canceled, with Applicants reserving the right to file continuing

applications directed to canceled subject matter. Therefore, withdrawal of the rejection is respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

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Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

856-810-1515